PROJECT DESCRIPTION

(85)

THE ADDICTION LIABILITY OF SYNTHETIC SUBSTITUTES FOR CODEINE.

Request for renewal of NR 113-149

1. Background Information

Since July 1951 a project, designed to develop a synthetic drug which would be as safe as codeine from the points of view of toxicology, antitussive activity and addiction liability as is codeine, has been carried on within the National Institute of Mental Health Addiction Research Center, Public Health Service Hospital, Lexington, Kentucky. This project has been financed in large part by funds from the Office of Naval Research.

A synthetic substitute for codeine is badly needed since opium, or morphine derived from opium, constitutes the only source of codeine. This means that, unless a synthetic is developed, the United States must continue to stockpile opium against the possibility of opium supplies being cut off during war. The importance of the project in relationship to the national defense is therefore obvious; but, unfortunately the facilities of the NIMH Addiction Research Center are not sufficient to carry out the work unless additional funds are supplied by the Department of Defense.

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II. Work Accomplished to Date

This is summarized in the Annual Progress Report sent to Dr. F. H. Quimby, Head of the Physiology Branch, Office of Naval Research, in January 1954.

The most promising drug yet developed in the program is the dextrorotatory 3-methylether of N-methylmorphinan. This compound is completely devoid of addiction liability and is of sufficiently low toxicity to be safe for human use. In experimental animals it has considerable antitussive activity and trial for antitussive activity under clinical conditions is now underway. The results obtained with this drug as a clinical antitussive are still conflicting and it is not yet certain whether it would be an adequate substitute for codeine for this purpose. It is also known that the drug is completely ineffective as an analgesic and would not serve as a substitute for codeine for this purpose.

Dl, d, and l 2-2-diphenylaminoethyl valerates have been shown to possess addiction liability similar to that of codeine. Preliminary clinical trials with these drugs have been recommended.

Dl-2-2-diphenyl-4-dimethylamine butyrate has properties similar to those of the valerates described in the preceding paragraph and, therefore, may serve as a substitute for codeine.

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D-2,N-dimethyl-hydroxy-morphinan is completely inert in man and devoid of addiction liability. The leverotatory form of this drug has mild morphine-like effects and partially suppresses abstinence from morphine. Its addiction liability is probably somewhat greater than that of codeine and, on the other hand, is far less than that of morphine. Depending on the outcome of clinical trials with the d-methylether of Dromoran, the compound might be considered as a potential substitute for codeine. It has one advantage over d-methyl Dromoran in that it will probably be a mild analgesic drug similar to codeine. Work with these compounds is still continuing.

4-4-diphenyl-6-dimethylamino-hexanone-3, a member of the methadone group, will apparently have addiction liability of a low order. This compound is in use in Germany as an antitussive and further work with it is imperative.

III. Need for Continuation of the Project

Although seven compounds that have potentialities as codeine substitutes have been uncovered by the program, only one of these so far is in clinical trial and it is unknown whether they will prove satisfactory in clinical use. The more compounds developed, the greater will be the chances of finding an adequate codeine substitute.

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IV. Work Proposed

During the period July 1954 to July 1955 we hope to complete the work on the isomers of 2,N-dimethylmorphinan and on 4-4-diphenyl-6-dimethylamino-hexanone-3. In addition to this, we hope to examine the potentialities of the myristyl ester of morphine and of 3-hydroxy-N-methylmorphinan.

Two new approaches to the problem will be explored. One of these consists of attempts to attenuate the potency and addiction liability of the synthetic drugs methadone and Dromoran by mixing them with specific antagonists, N-allylnormorphine and N-allylnordromoran, and such other antagonists as may be recommended by the Drug Addiction Committee of the National Research Council. In this connection it may be necessary to study the properties of a number of new antagonists in the hope of finding antagonists which are orally effective. The following antagonists will be examined: (1) N-allylnordiacetylmorphine, (2) N-propyl-dihydronormorphine, (3) dextro- and levorotatory-N-allylnordromoran, (4) levorotatory-3-methyl-ether of N-allylnordromoran, (5) levorotatory-N-propargyl-nordromoran, and (6) levorotatory-3-acetoxy-N-allylnordromoran.

The second approach will be to investigate the possibility of extending the supply of codeine by combining it with a metabolic blocking agent, beta-diethylaminoethylpropyl acetate, which has

been reported to increase the potency and length of action of analgesic drugs in animals.

V. Methods

The methods to be used are the standard addiction liability testing methods of the NIMH Addiction Research Center. These have been described in detail in previous project descriptions and in previous Annual Reports. For details these should be consulted.

VI. Evaluation of Data

The evaluation of data has also been discussed in previous descriptions which should be consulted.

VII. Location of Project

The work will be carried out at the NIMH Addiction Research Center, Public Health Service Hospital, Lexington, Kentucky. This institution provides the two necessary facilities for the type of work to be undertaken: (1) a pool of patients who will volunteer for the experiments with drugs, and (2) strict environmental control, which prevents the introduction of drugs other than those under study, into the experimental situation.

VIII. Experimental Personnel

The work will be carried out under the direction of Harris Isbell, M.D., Director of Research, NIMH Addiction Research Center. This investigator has had ten years of experience in research in narcotic drug addiction and has published many papers in the field. He will be assisted by two other experienced physicians, Dr. H. F. Fraser and Dr. Abraham Wikler, both of whom have had extensive experience in research in addiction. In addition to these medical personnel, the part-time services of a Biochemist and Research Psychologist will be made available. A special ward for conducting the studies is currently in operation.

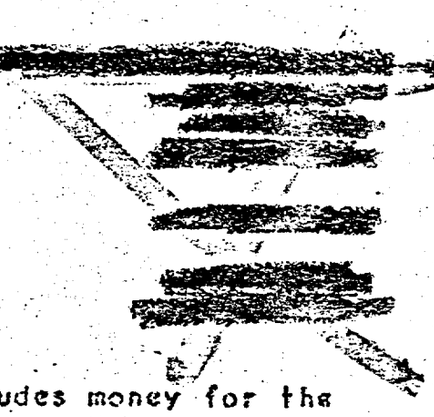
IX. Estimated Cost

1. Personnel

   6 Psychiatric Aide, GS-5
   1 Physical Science Aide, GS-4
   1 Physiologist, GS-7

2. Reserve for night, holiday and overtime pay

3. Miscellaneous expenses
   Total



Item 3, miscellaneous expenses, includes money for the purchase of drugs, chemicals, glassware, electroencephalographic and photographic paper, needles, syringes, etc.

Harris Isbell, M.D.
Director of Research

HI:rn

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